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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/218,660	12/22/1998	EVAN C. UNGER	UNGR-1520	2775

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EXAMINER	
SHARAREH, SHAHNAM J	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 01/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/218,660	UNGER ET AL.	
	Examiner	Art Unit	
	Shahnam Sharareh	1617	

-- The MAILING DATE of this communication appears on the cover sh et with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *100, 102, 103, 127, 194-200, 203, 210-228, 294-300, 303, 310-329, 331-337, 347-356, 412* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Continu d Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 24, 2003 has been entered.

Claims 100, 102, 103, 127, 194-200, 203, 210-228, 294-300, 303, 310-329, 331-337, 347-356, 412 are pending. Applicant is requested to provide a copy of all pending claims in response to this Office Action and clarify the status of claims 301-302, 304-309, 330, 338-346.

Priority

2. The effective priority date used for the examination of the instant application is May 1, 1996.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

3. Claims 100, 102-103, 127, 194-200, 203, 210-220, 294-300, 303, 310-317, 326-337, 347-350, 412 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grinstaff US Patent 5,498,421 (Grinstaff) in view of Wallach US Patent 4,853,228 and Allen US Patent 5,620,689.

The instant claims are directed toward a formulation comprising targeted phospholipid containing vesicles comprising a substantially insoluble gas, a linking group and a targeting ligand, wherein the linking group is a hydrophilic polymer that is covalently bound to both the surface of the lipid vesicle and said targeting ligand and is selected from a group consisting of PEG, polypropylene glycol, polyvinylalcohol. PVP, and copolymers thereof and wherein the vesicle is substantially free of crosslinked proteins and polymers. As defined by the instant specification at page 18, line 8-10, "substantially" refers to a measurement of greater than about 50%. Thus, such recitation is construed as the quantity and degree of cross-linking.

Grinstaff discloses a composition for in vivo delivery of a diagnostic or therapeutic agents comprising polymeric shell microbubbles (see col 7-8). Grinstaff teaches that the polymeric shell may be modified to include suitable agents, such as

phospholipid (including Phosphotidylethnolamine "PE"). Grinstaff also states that various polymers such as polyalkylene and protein for targeting which may be covalently bound to his shell, (see col 12, lines 14+). Grinstaff uses perfluorocarbons, which inherently possess the same solubility and boiling properties as the instant gases. Thus, Grinstaff's microbubbles meet the limitations of the instant lipid vesicles.

Grinstaff specifically teaches the conjugation of a targeting moiety to polymeric shell to provide advantage of site-specific delivery of the diagnostic or therapeutic microbubbles (col 8-9). Grinstaff does not explicitly teach a linker that is attached to his polymeric shell via a covalent linkage.

Wallace and Allen are used to show that covalent linkage between a lipid vesicle and a targeting ligand via a polymeric linker is conventional in the art. Wallace discloses a composition comprising lipid vesicles such as liposomes, which are used to the delivery of diagnostic or therapeutic agents, (see col 5, lines 8-20). Wallach also teaches that such lipid vesicles may be conjugated to targeting ligands such as peptides to provide the advantage of in vivo site specificity, (see col 4, lines 61+). Wallach specifically teaches that the targeting ligand may be conjugated to the microspheres by covalent attachment of the targeting molecule to the amino group of PE via a spacer group of polyoxyethylene head groups, (see col 5, lines 1-7).

Allen discloses a composition comprising lipid vesicles such as liposomes which are used for delivery of diagnostic or therapeutic agents. Allen discloses that the liposomes shell may be formed from a phospholipid such as PE, (see entire col 6-8). Attached to the vesicle shell is a polymer chain in which a ligand (antibody) is covalently

bound thereto, (see col 5-6; fig. 1, col 12, lines 29-34). Wallace and Allen do not teach gas containing vesicles.

Since Grinstaff, Wallach and Allen all disclose compositions comprising targeted lipid-coated vesicles for in vivo delivery of a diagnostic or therapeutic agents, they are viewed to be in the same field of endeavor.

It would have been obvious to one of ordinary skill in the art at the time of invention to modify the vesicle compositions of Grinstaff to include a targeting moiety via a linking group bound to the vesicle by a covalent linkage, because Grinstaff suggests that a targeting moiety can be attached to the phospholipid walls of lipid vesicles, and as taught by Wallace and Allen a such targeting moieties can be attached to covalently bound to the vesicle by a polymeric linking group. The ordinary skill in the art would have performed such modifications on Grinstaffs' vesicles because he would have had a reasonable expectation of success in improving the targeting and specificity of the lipid vesicle's activity.

Subsequently, as the instant methods require a mere in vivo application of the claimed compositions, it would have been obvious to one of ordinary skill in the art at the time of invention to administer such compositions in vivo for their preferred utility.

4. Claims 100, 102-103, 127, 194-200, 203, 210-220, 294-300, 303, 310-317, 326-337, 347-350, 412 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wallace and Allen in view of Schneider US Patent 5,643,553 (Schneider) and Porter US Patent 5,648,098 (Porter).

The teachings of Wallach and Allen are previously described. Wallach and Allen primarily teach all the limitations of the instant formulation except that they do not employ gaseous perfluorocarbons in their compositions. Wallace discloses a composition comprising lipid vesicles such as liposomes, which are used to the delivery of diagnostic or therapeutic agents, (see col 5, lines 8-20). Wallach also teaches that such lipid vesicles may be conjugated to targeting ligands such as peptides to provide the advantage of in vivo site specificity, (see col 4, lines 61+). Wallach teaches that the targeting ligand may be conjugated to the microspheres by covalent attachment of the targeting molecule to the amino group of PE via a spacer group of polyoxyethylene head groups, (see col 5, lines 1-7).

Allen discloses a composition comprising vesicles such as liposomes which are used for delivery of diagnostic or therapeutic agents. Allen discloses that the liposomes shell may be formed from a phospholipid such as PE, (see entire col 6-8). Attached to the vesicle shell is a polymer chain in which a ligand (antibody) is covalently bound (see col 5-6; fig. 1, col 12, lines 29-34).

The use of gaseous perfluorocarbons in combination with drug delivery vesicles has been well established in the art. Schneider for example teaches liposomal composition comprising gas-filled microbubbles, wherein the microbubbles may contain various surfactant such as a microbubble shell forming phospholipid or more specifically PE, as well as, polymeric surfactants, such as PEG surfactants, (col 6, lines 25-64; claims 4-20). Schneider also teaches that targeting ligands (g.g, polypeptides, antibodies, etc..) may be bounded by the stabilizing surfactant layer of the microbubbles

to provide site-specific targeting of the diagnostic or therapeutic microbubbles (see col 9, lines 10 +, example 11). Thus, Schneider teaches microbubbles that comprise PE shells combined with a PEG surfactant, which may be bound with a peptide targeting ligand. Schneider does not explicitly teach a perfluorinated gaseous liposome that is covalently bound to a targeting ligand via a PEG linker, but Porter teaches enhance drug activity when gaseous microbubbles contain perfluorinated gas.

Since it is *prima facie* obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; idea of combining them flows logically from their having been individually taught in prior art; thus, claims that require no more than mixing together of two conventional compositions are prima facie obvious subject matter. See *In re Kerkhoven*, 205 USPQ 1069(CCPA) 1980.

Thus, although Wallach and Allen do not specifically employ gas within their liposomal moieties, it would have been obvious to one of ordinary skill in the art at the time of invention to employ a perfluorinated gas with the liposomes' of Wallach or Allan because as taught by Schneider gaseous vesicles improve drug delivery of an agent and further as shown by Porter, perfluorinated gases are suitable gases for drug delivery compositions. Therefore, as reasoned in *In re Kerkhoven* mere mixing two conventional compositions for the same intended use would have been *prima facia* obvious. Therefore, one of ordinary skill in the art would have had a reasonable expectation of success when employing a perfluorinated gas with the liposomes of Wallach or Allen.

5. Claims 100, 102-103, 127, 194-200, 203, 210-220, 294-300, 303, 310-317, 326-337, 347-350, 412 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grinstaff in view of Wallach and Allen and further in view of Ginsburg US Patent 5,656,442 (Ginsburg).

The combination of Grinstaff, Wallach and Allen are described above. Such combination does not teach the specific targeting group of Arg-Gly-Asp ("RGD") or Lys-Gln-Ala-Gly-Asp-Val.

Ginsburg discloses the synthetic alpha-amino acid containing chains of Lys-Gln-Ala-Gly-Asp-Val or RGD (col 33, lines 45-55). Ginsburg further teaches that such amino-acid chains specifically bind to fibrinogen of the platelet membrane glycoprotein complex IIb/IIIa receptor and that they can be used as a targeting ligand in an in vitro kit (abstract).

Although the combination of the teachings of Grinstaff, Wallach or Allen does not specifically teach the use of Lys-Gln-Ala-Gly-Asp-Val or RGD as a targeting agent, they suggest the use of any suitable targeting agent to improve specificity of their drug delivery system. Accordingly, it would have been obvious to one of ordinary skill in the art at the time of invention to use a suitable targeting agent such as those taught by Ginsburg, because the ordinary artisan would have had a reasonable expectation of success to improve specificity of a drug delivery vesicles to platelet membranes when employing Ginsburgs' targeting agents.

6. Claims 100, 102, 103, 127, 194-200, 203, 210-228, 294-300, 303, 310-329, 331-337, 347-356, 412 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wallach and Allen in view of Schneider and Porter and further in view of Ginsburg.

The combination of the teachings of Wallach, Allen, Schneider and Porter are described above. Such combination does not teach the specific targeting group of Arg-Gly-Asp ("RGD") or Lys-Gln-Ala-Gly-Asp-Val.

Ginsburg discloses the synthetic alpha-amino acid containing chains of Lys-Gln-Ala-Gly-Asp-Val or RGD (col 33, lines 45-55).

Since Wallach, Allen, Schneider, Porter and Ginsberg all disclose compositions comprising targeted lipid-coated vesicles for in vivo delivery of a diagnostic or therapeutic agents, they are viewed to be in the same field of endeavor.

Although the combination of the teachings of Wallach or Allen does not specifically teach the use of Lys-Gln-Ala-Gly-Asp-Val or RGD as a targeting agent, they suggest the use of any suitable targeting agent to improve specificity of their drug delivery system. Accordingly, it would have been obvious to one of ordinary skill in the art at the time of invention to use a suitable targeting agent such as those taught by Ginsburg, because the ordinary artisan would have had a reasonable expectation of success to improve specificity of a drug delivery vesicles to platelet membranes when employing Ginsburgs' targeting agents.

Response to Arguments

7. Applicant's arguments filed Ocotber 14, 2003 have been fully considered but they are not persuasive. Applicant argues that the instant claims are now directed to flexible vesicles and insoluble gases which are not described in the cited references.

In response Examiner states that such characteristics are functional and inherent to the nature of the gas or vesicles employed. Since prior art teach the same gas or vesicle material, they also provide for their functional characteristics.

Conclusion

8. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shahnam Sharareh whose telephone number is 703-306-5400. The examiner can normally be reached on 8:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, PhD can be reached on 703-308-1877. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1123

RUSSELL TRAVERS
PRIMARY EXAMINER

Continuation of Disposition of Claims: Claims pending in the application are 100,102,103,127,194-200,203,210-228,294-300,303,310-329,331-337,347-356 and 412.